REMARKS

Claims 1-31 are pending in the above-referenced patent application. With entry of this Amendment, the specification has been amended to correct a minor typographical error noted by the applicant. Claims 1 and 16 have been amended to more precisely define the claimed methods. The dependency of Claim 12 has been amended. Claim 12 now depends on Claim 9. Dependencies of Claims 21, 22, 24, 25 and 28-31 have been amended. Claims 21, 22, 24, 25 and 28-31 now depend on Claim 19. No new matter has been introduced by this amendment. Reconsideration is respectfully requested.

Claim Objection

Claim 12 is objected because the term "divalent cation" is lacking antecedent basis. Applicants have amended Claim 12 to change its dependency. Claim 12 now depend on Claim 9. Applicants believe that this amendment overcomes the Examiner's objection.

Reconsideration and withdrawal of the objection are respectfully requested.

Claim Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-31 are rejected under 35 U.S.C. § 112, first paragraph, as not enabled for "the general treatment of a patient who is suffering from a cytokine-mediated inflammatory condition".

Applicants amended Claims 1 and 16 according to the Examiner's suggestion. Applicants believe that this amendment overcomes the Examiner's rejection.

Reconsideration and withdrawal of the objection are respectfully requested.

Claim Rejection under 35 U.S.C. § 102(e)

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,417,231 ("Greenway"). Applicants respectfully traverse the rejection.

Greenway does not teach or suggest each and every element in the claimed invention. The claimed invention recites a novel method of using a composition including an ester of an alpha-ketoalkanoic acid for treating specified cytokine-mediated inflammatory diseases. In

particular, the claimed diseases are rheumatoid spondylitis, osteoarthritis, gouty arthritis, endotoxic shock, cerebral malaria, silicosis, pulmonary sarcoidosis, bone resorption disease, graft versus host disease, allograft rejections, fever and myalgia due to infection, AIDS related complex (ARC), Crohn's disease, rheumatoid arthritis, cachexia and septic shock.

In contrast, Greenway discloses the use of glyceryl esters of pyruvic acid, such as tripyruvin, as "a way to deliver pyruvate" (column 4, lines 51-52). Greenway further discloses that a composition comprising tripyruvin, in some embodiments in combination with a bronchodilating agent, can be administered in the form of an aerosol for ameliorating asthma (column 5, lines 34-42). Asthma, however, is not an element of Claim 1. Nor are any of the diseases recited in Claim 1 of the instant application taught by Greenway. As each and every element of the invention of Claim 1 is not disclosed in Greenway, Applicants submit Claim 1 as well as Claims 2, 4 and 5, dependent thereon, are novel over Greenway.

Reconsideration and withdrawal of the objection are respectfully requested.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 4-13, 15-17 and 19-31 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,798,388 ("Katz") in view of U.S. Patent Application Publication No. 2003/0073743 ("Ajami"). Katz is relied on by the Examiner as allegedly teaching a method for treating cytokine-mediated inflammatory diseases by administering pyruvate precursors, some of which are allegedly pyruvate esters. Ajami is relied on by the Examiner as allegedly teaching the use of pyruvic acid esters of the present invention. The Examiner takes the position that it would have been obvious to one of the ordinary skill in the art to employ the pyruvic esters disclosed in Ajami and to use the teachings described in Katz to treat cytokine-mediated inflammatory diseases. Applicants respectfully traverse the rejection.

Applicants respectfully submit that one skilled in the art would not be motivated to combine the cited references to arrive at the claimed invention.

Katz teaches the use of pyruvate or pyruvate precursors to treat inflammatory responses. However, the pyruvates taught by Katz are pyruvic acid or salts of pyruvic acid:

> The preferred inflammatory mediator is at least one compound selected from the group consisting of a pyruvate precursor, pyruvate, a lactate precursor and lactate. [...]

> Preferably the pyruvate is selected from the group consisting of pyruvic acid, lithium pyruvate, sodium pyruvate, potassium pyruvate, magnesium pyruvate, calcium pyruvate, zinc pyruvate, manganese pyruvate, and the like and mixtures thereof. Sodium pyruvate is most preferred.

(column 7, lines 21-30). Furthermore, the pyruvate precursors taught in Katz are amides of pyruvic acid:

> "Another preferred inflammatory mediator is selected from the pyruvate precursors consisting of pyruvyl-glycene, pyruvyl-alanine, pyruvyl-leucine, pyruvyl-valine, pyruvyl-isoleucine, pyruvyl-phenylalanine, pyruvamide, dihydroxyacetone ..."

(Column 7, lines 31-35.)

Katz does not teach that pyruvates or the precursors of pyruvic acid are pyruvate esters. Hence, there is no teaching or suggestion in Katz to use pyruvate esters for treating cytokine-mediated inflammatory diseases.

Ajami fails to provide the teachings that are lacking in Katz. Ajami discloses a composition comprising esters of pyruvic acid and an enolization agent for the treatment of ischemic conditions. Ajami does not teach the treatment of cytokine-mediated inflammatory diseases using esters of pyruvic acid.

Neither Katz nor Ajami, independently or in combination, teach that esters of pyruvic acid can be utilized to treat cytokine-mediated inflammatory diseases. One having ordinary skill would not have been motivated to replace the pyruvic acid, pyruvic acid salts or pyruvic acid amides taught by Katz for the treatment of inflammatory responses with the pyruvate esters taught by Ajami for the treatment of ischemic conditions. One skilled in the art would not look to a reference such as Ajami, teaching treatment for ischemic diseases, for guidance in treating inflammatory diseases. Therefore, the skilled person would not be motivated to modify the methods disclosed in Katz based on the teachings of Ajami. As such, the claimed invention is non-obvious over the combined teachings of those two references

Applicants further submit that the present invention is non-obvious over the combination of Katz and Ajami for other reasons. Namely, the esters of pyruvic acid exhibit unexpectedly superior anti-inflammatory properties in treating cytokine-mediated inflammatory disorders when compared to pyruvic acid salts.

To support this assertion, the applicants provide herewith a Declaration of Dr. Mitchell P. Fink under 37 C.F.R. 1.132, (hereinafter, the "Fink Declaration"), which provides the results of side-by-side comparison of pyruvic acid salts and ethyl pyruvate in an *in vitro* animal model of inflammation. The Fink Declaration expands the scope of and supplements the data presented in Examples 1 through 8 of the instant application and further provides evidence that ethyl pyruvate is more effective than pyruvic acid in ameliorating the effect of inflammation on intestinal mucosa and that ethyl pyruvate but not sodium pyruvate inhibits cytokine-induced expression of ICAM-1, a receptor implicated in recruitment of leukocytes by the inflamed tissues.

The Fink Declaration shows that ethyl pyruvate provided far superior protection than sodium pyruvate against LPS-induced gut barrier dysfunction as measured by ileal mucosal hyperpermeability. When similar amounts of either pyruvate or sodium pyruvate were administered to mice after induction of gut barrier dysfunction by LPS injections,, ethyl pyruvate showed nearly 10-fold higher inhibition of mucosal permeability than sodium pyruvate (Fink Declaration, Section 5, FIG. 1).. Ethyl pyruvate also provided better protection than sodium pyruvate against LPS-induced gut barrier dysfunction as measured by induction of *iNOS* and increased production of *NO*·. These results are presented in Section 5, FIGs. 2A and 2B of the Fink Declaration.

The Fink Declaration further provides evidence that ethyl pyruvate is highly effective in inhibiting the elevated levels of expression of ICAM-1 in cells stimulated by IL-1β. Surprisingly, and importantly, equivalent concentrations (on a millimole-for-millimole basis) of sodium pyruvate virtually failed to inhibit IL-1β-induced ICAM-1 expression in this assay system (i.e., sodium pyruvate was not an anti-inflammatory agent). These results are presented in Section 6 of the Fink Declaration.

Based on this evidence, it is apparent that ethyl pyruvate unexpectedly possesses therapeutic properties that are superior to those of pyruvic acid salts.

Applicants submit that neither Katz nor Ajami provide any suggestion or motivation to combine the teachings of these references. Further, Applicants submit that the pyruvate esters of the instant invention possess unexpected advantages over the compounds and methods of Katz and Ajami because, as shown by the Fink Declaration, they are superior to pyruvic acid salts in treating cytokine-mediated inflammatory disorders. Thus, the Fink Declaration presents the

results of three experiments. In all three, ethyl pyruvate is more effective than sodium pyruvate in alleviating the symptoms of cytokine-mediated inflammatory conditions. In one experiment, ethyl pyruvate is nearly 10-fold more effective than sodium pyruvate. In another experiment, ethyl pyruvate showed significant anti-inflammatory activity, while sodium pyruvate showed virtually none.

Accordingly, Claims 1, 2, 4-13, 15-17 and 19-31 are not rendered obvious by Katz in view of Ajami or, in the alternative, the *prima facie* case of obviousness is overcome.

Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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